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Evaluation of the ultrasonication process for injectability of hydraulic calcium phosphate pastes

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ABSTRACT

This study examined the use of ultrasonication to improve the injectability of an aqueous calcium phosphate paste. Ultrasonication was applied to the paste through the plunger of the delivery syringe. A factorial design of experiments with three investigated factors, liquid to powder ratio (LPR) (38%, 39% and 40%), the size of the delivery syringe (5 and 10 ml) and the amplitude of the 20 kHz power ultrasonication (0–30 μm), was used in this study. The volume fraction of the extruded paste was used to quantify injectability. Small injectability improvements were observed with an increase in LPR and decrease in syringe size, which is consistent with previously published results. The improvements due to ultrasonication were significant and remarkable. For example, when using the 5 ml syringe the injected volume fraction of the 38% LPR paste improved from 63.4 ± 2.3% without ultrasonication to 97.3 ± 2.4% with 30%. This result shows that ultrasonication is an effective solution to improve injectability.

1. Introduction

The poor injectability of calcium phosphate (CaP) pastes is an important limitation in the use of such pastes as bone graft substitutes [1–6]. Recent studies have shown that the poor injectability results from separation of the liquid and solid particles under the injection pressure, eventually leading to a halt of the injection process [1–3]. Bohner and Baroud [1] postulated that there is competition between the filtration process and flow of the paste through the thin cannula. Specifically, the delivery pressure applied to the hydraulic paste forces flow of the paste itself but, at the same time, the liquid phase is more mobile than the particles and is expelled at a faster rate than the solid particles. Bohner and Baroud [1] demonstrated experimentally these observations using a calcium phosphate hydraulic paste and examined the relations between several parameters of the delivery process and the paste volume fraction extruded. Additionally, Habib et al. [2] investigated the water content and the distribution of paste left in the delivery syringe and of the extrudate. This study showed that a water gradient exists in the paste left in the syringe, with a higher water content near the syringe tip and a lower water content near the syringe plunger, suggesting that poor injectability is due to the formation of a plug on the plunger side.

Earlier research studies focused on the use of chemical additives to improve paste injectability and significant attention was given to examining the injectability of thick pastes and the required delivery force [4–6]. In particular, ionic modifiers such as trisodium citrate solution were added to the calcium phosphate paste to decrease the viscosity and, therefore, improve the paste injectability [4]. However, this strategy generally leads to very liquid pastes with poor cohesion, which may have dramatic consequences upon implantation, for example for vertebroplasty (risk of leakage). Alternatively, steric modifiers such as xanthan gum alter the interaction between the particles and enhance the injectability, partially due to the viscosity increase of the dispersing medium [5]. High viscosity dispersing liquids are less mobile and, therefore, reduce the filtration process. Injectability was accordingly improved by adding sodium glycerophosphate (NaGP), lactic acid, and glycerol [6]. Chitosan slightly improved injectability, as reported by Leroux et al. [6]. However, cost, sterilization, and biocompatibility are some of the main concerns when using such additives.

Beside chemical approaches, physical approaches have also been used to enhance injectability, for example by optimizing the particle size distribution (PSD) [1,5,7–9]. Bohner and Baroud [1] predicted that a decrease in mean particle size should improve injectability. This result was confirmed by Baroud et al. [5] and Gbureck et al. [7]. However, the mechanisms were slightly different. Whereas Baroud et al. [5] observed an increase in paste viscosity and yield stress with a decrease of in particle size,

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Gbureck et al. [7] noticed a decrease in paste viscosity. In the former case a very large fraction of small particles was generated, whereas in the latter case only a very small amount formed. Even though there is a fairly good understanding of these effects [8,9], these results underline the complexity of the link between PSD and paste rheological properties.

This study focuses on an alternative and novel approach to improve the injectability of CaP pastes. It involves the use of mechanical energy to agitate the particles in the paste, modifying the rheological properties of the paste and, therefore, the injectability. This is neither based on a change in particle size or shape or size distribution, nor on a change in composition. Specifically, ultrasound energy has been reported as an effective means for dispersing and deagglomerating pastes, leading to a decrease in paste viscosity [10,11].

High power ultrasonication involves relatively high amplitudes [10–13], typically ranging between 5 and 50 μm [12,13]. Yet, high power applications tend to use frequencies at the low end of the ultrasound spectrum (i.e. from 20 to 100 kHz). The known effects of ultrasonication include heat generation, cavitation, deagglomeration and shear thinning. Specifically, acoustic energy irradiated from a probe tip produces sound waves propagating into the liquid medium, resulting in alternating high pressure (compression) and low pressure (rarefaction) cycles, possibly leading to the formation of gas bubbles (cavitation). This leads to oscillating mechanical stress on the particles that are attracted by the electrostatic forces [15]. Also, ultrasonic cavitation in liquids is known to cause high speed liquid flow that can cause separation of the flowing liquid from the particles and high pressure between the particles that could separate them from each other. Smaller particles are accelerated with the liquid flow and this causes collisions at high speeds [15–17]. Li et al. [18] used ultrasonication to prepare polymer–silicate nanocomposites during extrusion and showed that ultrasonication decreased the size and distribution of clay particles in the polymer matrix because it prevents the agglomeration of clay particles during the extrusion process [18].

This study hypothesizes that ultrasonication applied to CaP pastes during delivery improves dispersion of the powder particles, improves the paste flow properties and, therefore, increases the volume fraction that can be extruded. An experimental plan has been designed in order to examine this hypothesis in a laboratory setting.

2. Materials and methods

2.1. Model paste and compositions

β-Tricalcium phosphate (β-TCP) ($Ca_3(PO_4)_2$, No. 21218, Fluka, Buchs, Switzerland) was admixed with distilled water to produce a model paste. This paste has three interesting features. First, it is non-setting and, hence, does not have transient rheological properties like calcium phosphate cements, which produces controlled conditions for the study [5]. Second, the selected β-TCP powder has morphological features such as particle size, distribution and specific surface area typical for calcium phosphate powders used in commercial calcium phosphate cement formulations. Third, previous studies have shown that this β-TCP-based paste produces a significant filter pressing effect [5]. The LPR of the pastes used here were 38, 39 and 40 wt.%. These compositions form poorly injectable pastes over a broad injectability range [1,2].

2.2. Electronically assisted delivery device

The experimental set-up contains four important parts: the ultrasonic processor, the transducer, the sonotrode probe, and the plunger (Fig. 1). The following paragraphs describe these four parts in more detail.

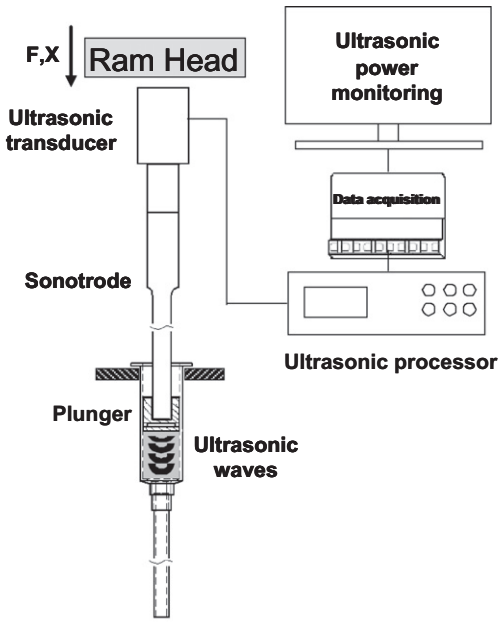

Fig. 1. Schematic of the experimental set-up.

The ultrasonic processor (130 W, 20 kHz, Cole-Parmer, Vernon Hills, IL) converts the electric power to the frequency, voltage and current required by the ultrasonic system. Further, the device allows control of the ultrasonic amplitude. The ultrasonic processor is able to produce up to 130 kW power at a frequency of 20 kHz. It is equipped with an interface to enable external power monitoring though an external computer. Specifically, the power signal was magnified using a signal conditioner, monitored through a data acquisition card and a labview interface. The transducer converts the electrical power to mechanical power in the form of vibrations [19]. The sonotrode, also referred to as the probe, 6 mm in diameter and 113 mm long, was geometrically fitted to the syringe plungers. The syringe plungers are made of Delrin and are used in 5 and 10 ml syringes. The 100% amplitude of the probe corresponded to a distance of 150 μm. Selection of the ultrasonication amplitudes was subjected to two main constraints. First, the ultrasonic processor could not produce an amplitude smaller than 20% (= 30 μm). Second, overheating of the plunger occurred rapidly at large amplitudes. So the following amplitudes were selected: 0%, 20%, 25% and 30%.

2.3. Injectability test

The injectability tests were performed using a 858 Mini Bionix II testing system (MTS Systems Corp., Eden Prairie, MN) using a 1.25 mm min^{-1} constant ram speed (i.e. 2.5 and 1.8 ml min^{-1} volume flow rate using 10 and 5 ml syringes, respectively). This low injection rate is normally used in vertebroplasty and for the paste compositions chosen here promotes the phase separation phenomenon [2]. An 8 gauge cannula of 100 mm length and 3.2 mm inner diameter was attached to a 5 or 10 ml syringe (CODAN Medical ApS, Espergærde, Denmark) to simulate delivery through the thin cannula. Special fixtures were designed to hold the ultrasonic probe perpendicular to the syringe plunger (Fig. 1). In particular, the MTS ram applied a controlled displacement to the ultrasonic probe, which in turn transmitted it to the syringe plunger. The MTS also measured the reaction force in relation to the displacement. A specially designed set-up was used to ensure good contact

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